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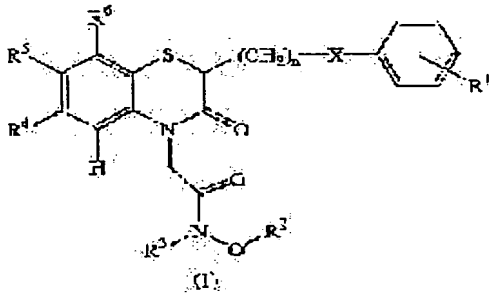
(54) BENZOTHIAZIN-3-ONE DERIVATIVE

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a medicine useful for treating and preventing articular diseases such as osteoarthritis and chronic rheumarthritis, cancer cell metastasis, gingivitis and the like.
SOLUTION: This benzothiadin-3-one derivative is represented by formula (1) [X is a single bond or a heterogeneous atom; (n) is an integer of 1 to 6; R1 is H, a halogen atom or a substituent; R2 is H or a substituent; R3 is H or a substituent (R2 and R3 are simultaneously not H) or R2 and R3 are bound to form a heterogeneous ring; R4, R5 and R6 are each a substituent] or its salt.



LEGAL STATUS

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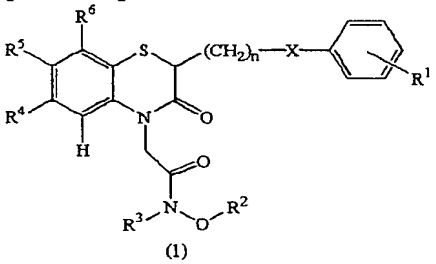
CLAIMS

[Claim(s)]
[Claim 1] Formula (1)
[Formula 1]



(1)

(X expresses single bond, a sulfur atom, or an oxygen atom among a formula. n) The integer of 1 to 6 is expressed. R1 A hydrogen atom, a halogen atom, the alkyl group that may be permuted, The alkoxy group which may be permuted, an alkyl sulfonyl group, the aryloxy group which may be permuted, or the heteroaryloxy radical which may be permuted is expressed. R2 A hydrogen atom, the alkyloxy carbonyl which may be permuted, the alkyl which may be permuted, Or [R3 expresses / whether it expresses the carbamoyl group which may be permuted, or the annular carbamoyl group which may be permuted, or / a hydrogen atom, the alkyloxy carbonyl which may be permuted, or the alkyl which may be permuted (however, R2 and R3 do not become a hydrogen atom at coincidence)] R2 and R3 join together and heterocycle is expressed. Or R4 A hydrogen atom, a carboxy group, a tetrazolyl group, an imidazolyl radical, a permutation alkyl group, An alkyl sulfonyl group, the carbamoyl group which may be permuted, or the alkyloxy carbonyl group which may be permuted is expressed. R5 A hydrogen atom, a carboxy group, a tetrazolyl group, an imidazolyl radical, a permutation alkyl group, expressing an alkyl sulfonyl group, the carbamoyl group which may be permuted, the annular carbamoyl group which may be permuted, or the alkyloxy carbonyl group which may be permuted, R6 expresses a hydrogen atom, a carboxy group, or the alkyloxy carbonyl group that may be permuted. The benzothiazin-3-ON derivative expressed or its salt.
[Claim 2] The benzothiazin-3-ON derivative according to claim 1 whose n is the integer of 1 to 4, or its salt.
[Claim 3] The benzothiazin-3-ON derivative according to claim 1 or 2 whose R1 is a halogen atom, the alkoxy group which may be permuted, an alkyl sulfonyl group, the aryloxy group which may be permuted, or the heteroaryloxy radical which may be permuted, or its salt.
[Claim 4] The benzothiazin-3-ON derivative according to claim 3 whose X is single bond, or its salt.
[Claim 5] The benzothiazin-3-ON derivative according to claim 4 whose n is 1, or its salt.
[Claim 6] The benzothiazin-3-ON derivative according to claim 1 to 5 whose R4 is a carboxy group, a tetrazole radical, an imidazole group, a permutation alkyl group, an alkyl sulfonyl group, the carbamoyl group that may be permuted, or the alkyloxy carbonyl group which may be permuted, or its salt.
[Claim 7] The benzothiazin-3-ON derivative according to claim 1 to 5 whose R5 is a carboxy group, a tetrazole radical, an imidazole group, a permutation alkyl group, an alkyl sulfonyl group, the carbamoyl group that may be permuted, the annular carbamoyl group which may be permuted, or the alkyloxy carbonyl group which may be permuted, or its salt.
[Claim 8] The benzothiazin-3-ON derivative according to claim 1 to 7 whose R1 is a trifluoro methoxy group, or its salt.
[Claim 9] The benzothiazin-3-ON derivative according to claim 1 to 7 which is the aryloxy group by which R1 may be permuted, or its salt.
[Claim 10] The physic constituent containing a benzothiazin-3-ON derivative or its salt according to claim 1 to 9.
[Claim 11] The matrix METARO protease inhibitor which makes an active principle a benzothiazin-3-ON derivative or its salt according to claim 1 to 9.
[Claim 12] The articular disease therapy agent which makes an active principle a benzothiazin-3-ON derivative or its salt according to claim 1 to 9.
[Claim 13] The cancer transition inhibitor which makes an active principle a benzothiazin-3-ON derivative or its salt according to claim 1 to 9.
[Claim 14] The anti-inflammation therapy agent which makes an active principle a benzothiazin-3-ON derivative or

its salt according to claim 1 to 9.
[Claim 15] The periodontitis therapy agent which makes an active principle a benzothiazin-3-ON derivative or its salt according to claim 1 to 9.

[Translation done.]

TECHNICAL FIELD

[Industrial Application] This invention relates to a new benzothiazin-3-ON derivative or its salt. It is related with the new new benzothiazin-3-ON derivative which checks matrix METARO protease activity in in the living body in a detail. Furthermore, a detail is metabolized in in the living body, and it is related with the prodrug which checks matrix METARO protease activity.
[0002]

[Translation done.]

PRIOR ART

[Description of the Prior Art] a group to which the collagen and the extra-cellular matrix represented by the proteoglycan which constitutes connective tissue are called a matrix protease — it is metabolized with a proteolytic enzyme. The matrix METARO protease Collagenase (the matrix METARO protease -1, MMP-1), Gelatinase A (the matrix METARO protease -2, MMP-2) Stromelysin (the matrix METARO protease -3, MMP-3), Gelatinase B (the matrix METARO protease -9, MMP-9) Current [, such as collagenase 3 (the matrix METARO protease -13, MMP-13) and the film joint mold matrix METARO protease -1 (MT1-MMP, MMP-14), / 19 kinds of] are known. If an extra-cellular matrix is normal, they are composition of these matrix METARO proteases, and the level of secretion, or is strictly controlled by the internality inhibitor (for example, TIMP (Tissue Inhibitor of matrix metallo protease)) in the outside of a cell. There are many reports about the relation of the disease which makes a symptom protease activity rise produced when this balance collapses, and destruction of connective tissue.
[0003] for example, at the joint of the osteoarthritis and rheumatoid arthritis patient whose destruction of an articular cartilage is the description A matrix METARO protease, especially stromelysin, Collagenase is detected with a high level (). [Arthr.] Rheum., 33, and 388-397(1990); S. M.Krane etc. and "Modulation of matrix synthesis and degradation in joint inflammation, The Control of Tissue Damage", A.B.Glauert (Editor), Elsevier Sci.Publ., Amsterdam, 1988, and Ch.14, pp.179-195; Clin.Chim.Acta, 185, 73-80 (1989); Arthr.Rheum., 27, 305-312 (1984); J.Clin.Invest., 84, 678-685 (1989). In order for a cancer cell to permeate and transfer an organization and to form a secondary tumor Since the step which decomposes basement membrane is indispensable, the manifestation of matrix METARO proteases, such as Gelatinases A and B, and enzyme activity Infiltration of a cancer cell, related (FEBS J. —) to transition ability 5 and 2145-2154(1991); Trends Genet., 6, 121-125 (1990); Cancer Res., 46, 1-7 (1986); Cell, 64, 327-336 (1990); Cancer and Metastasis Rev., 9,305-319 (1990). It is checked in the fibrocyte taken out from the organization which has shown the symptoms of gingivitis that collagenase and stromelysin are activated (J. Periodontal Res., 16, 417-424 (1981)). Moreover, those enzyme level is related with the seriousness of gingivitis (J. Periodontal Res., 22, 81-88 (1987)).
[0004] Collagenase -3 (the matrix METARO protease -13, MMP-13) A chronic articular rheumatism patient's synovial membrane, The osteoarthritis discovered (J. — Clin.Invest., 97, 2011-2019(1996); J.Rheumatol., 23, and 509-595(1996); J.Biol.Chem. —) by the Homo sapiens chondrocyte whose symptoms are shown 271 23577-23581 (1996); J.Clin.Invest., 97, 761-768 (1996). Moreover, MMP-13 have the powerful decomposition activity over II mold collagen and AGURIKAN which are the main extra-cellular-matrix constituents of a cartilage matrix, and relation with the cartilage osteoarthritis and articular rheumatism is pointed out (J. Biol.Chem., 271, 1544-1550(1996); FEBS Lett., 380, 17-20 (1996)). Therefore, a matrix METARO protease inhibitor can be used as therapy agents, such as transition of articular diseases, such as osteoarthritis and rheumatoid arthritis, and a cancer cell, and gingivitis, and preventive. A matrix METARO protease besides destruction of the above extra-cellular matrices The conversion in the mature mold of a tumor necrosis factor from a potential mold (Nature, 370, 555-557 (1994)), Decomposition of the alpha 1-antitrypsin which is serine protease inhibitor (FEBS Lett., 279, 191-194 (1991)), It is participating in the activation (Biochemistry, 29, 10261-10670(1990); J.Biol.Chem., 267, 21712-21719 (1992)) by both matrix METARO proteases. Therefore, a matrix METARO protease inhibitor can be used as an anti-inflammatory agent. However, the matrix METARO protease inhibitor which shows activity sufficient as drugs to current is not known.
[0005]

[Translation done.]

* NOTICES *

EFFECT OF THE INVENTION

[Effect of the Invention] A new benzothiazin-3-ON derivative can be offered by this invention. Moreover, while this invention compound shows good oral absorbency, since it is metabolized in in the living body and matrix METARO protease inhibition activity is shown, this invention compound is useful as the therapy agent of articular diseases, such as osteoarthritis and rheumatoid arthritis, the transition inhibitor of a cancer cell, or an anti-inflammatory agent.

[Translation done.]

* NOTICES *

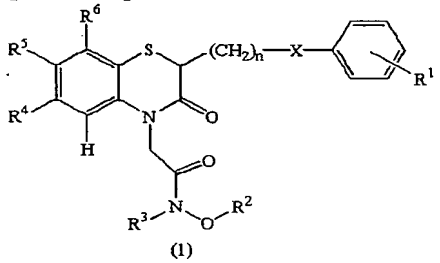
TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] The technical problem of this invention is in offer of drugs useful as therapy agents, such as transition of articular diseases, such as osteoarthritis and rheumatoid arthritis, and a cancer cell, and gingivitis, and preventive.
[0006]

[Translation done.]

MEANS

[Means for Solving the Problem] this invention persons are metabolized in in the living body, find out that it is the new prodrug which discovers matrix METARO protease inhibition activity, and came to complete this invention while the benzothiazin-3-ON derivative showed good oral absorbency, as a result of repeating examination wholeheartedly, in order to solve the above-mentioned technical problem.
[0007] That is, the invention in this application is the formula (1) of (1) following.
[Formula 2]



(1)

(X expresses single bond, a sulfur atom, or an oxygen atom among a formula. n) The integer of 1 to 6 is expressed. R1 A hydrogen atom, a halogen atom, the alkyl group that may be permuted, The alkoxy group which may be permuted, an alkyl sulfonyl group, the aryloxy group which may be permuted, or the heteroaryloxy radical which may be permuted is expressed. R2 A hydrogen atom, the alkyloxy carbonyl which may be permuted, the alkyl which may be permuted, Or [R3 expresses / whether it expresses the carbamoyl group which may be permuted, or the annular carbamoyl group which may be permuted, or / a hydrogen atom, the alkyloxy carbonyl which may be permuted, or the alkyl which may be permuted (however, R2 and R3 do not become a hydrogen atom at coincidence)] R2 and R3 join together and heterocycle is expressed. Or R4 A hydrogen atom, a carboxy group, a tetrazolyl group, an imidazolyl radical, a permutation alkyl group, An alkyl sulfonyl group, the carbamoyl group which may be permuted, or the alkyloxy carbonyl group which may be permuted is expressed. R5 A hydrogen atom, a carboxy group, a tetrazolyl group, an imidazolyl radical, a permutation alkyl group, expressing an alkyl sulfonyl group, the carbamoyl group which may be permuted, the annular carbamoyl group which may be permuted, or the alkyloxy carbonyl group which may be permuted, R6 expresses a hydrogen atom, a carboxy group, or the alkyloxy carbonyl group that may be permuted. The benzothiazin-3-ON derivative expressed or its salt.
(2) The benzothiazin-3-ON derivative or its salt of the above-mentioned (1) publication whose n is the integer of 1 to 4.
(3) A benzothiazin-3-ON derivative or its salt the above (1) whose R1 is a halogen atom, the alkoxy group which may be permuted, an alkyl sulfonyl group, the aryloxy group which may be permuted, or the heteroaryloxy radical which may be permuted, or given in (2).
(4) The benzothiazin-3-ON derivative or its salt of the above-mentioned (3) publication whose X is single bond.
(5) The benzothiazin-3-ON derivative or its salt of the above-mentioned (4) publication whose n is 1.
(6) A benzothiazin-3-ON derivative or its salt given in either of above-mentioned (1) - (5) whose R4 is a carboxy group, a tetrazole radical, an imidazole group, a permutation alkyl group, an alkyl sulfonyl group, the carbamoyl group that may be permuted, or the alkyloxy carbonyl group which may be permuted.
(7) A benzothiazin-3-ON derivative or its salt given in either of above-mentioned (1) - (5) whose R5 is a carboxy group, a tetrazole radical, an imidazole group, a permutation alkyl group, an alkyl sulfonyl group, the carbamoyl group that may be permuted, the annular carbamoyl group which may be permuted, or the alkyloxy carbonyl group which may be permuted.
(8) A benzothiazin-3-ON derivative or its salt given in either of above-mentioned (1) - (7) whose R1 is a trifluoro methoxy group.
(9) A benzothiazin-3-ON derivative or its salt given in either of above-mentioned (1) - (7) which is the aryloxy group by which R1 may be permuted.
[0008] (10) The above (1) Physic constituent which contains the benzothiazin-3-ON derivative of a publication, or its salt in either of - (9).
(11) The above (1) Matrix METARO protease inhibitor which makes an active principle the benzothiazin-3-ON

derivative of a publication, or its salt at either of - (9).
(12) The above (1) Articular disease therapy agent which makes an active principle the benzothiazin-3-ON derivative of a publication, or its salt at either of - (9).
(13) The above (1) Cancer transition inhibitor which makes an active principle the benzothiazin-3-ON derivative of a publication, or its salt at either of - (9).
(14) The above (1) Anti-inflammation therapy agent which makes an active principle the benzothiazin-3-ON derivative of a publication, or its salt at either of - (9).
(15) The above (1) Periodontitis therapy agent which makes an active principle the benzothiazin-3-ON derivative of a publication, or its salt at either of - (9).
(16) The above (1) Physic constituent for taking orally which contains the benzothiazin-3-ON derivative of a publication, or its salt in either of - (9). It is related with **.
[0009]
[Embodiment of the Invention] The substituent in this invention compound is explained below concretely. As an alkyl group in R1, the straight chain or branching alkyl group of carbon numbers 1-6 is mentioned, and, specifically, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 3-methylpropyl, 1, and 1-dimethyl ethyl, pentyl, hexyl, etc. are mentioned. As a substituent in the permutation alkyl group of R1 For example, a hydroxyl group, a halogen atom (for example, a fluorine, chlorine, a bromine, iodine, etc. are mentioned.) The alkoxy group of carbon numbers 1-6 (for example, the straight chain or branching alkoxy group of carbon numbers 1-6 is mentioned, and, specifically, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, 1, and 1-dimethylethoxy, pentoxy, HEKISOKISHI, etc. are mentioned.) etc. — it may be mentioned, an adjoining alkoxy group may join together, for example, a methylene dioxy radical and an ethylene dioxy radical may be formed. . as the number of the substituents in the permutation alkyl group of R1 — 1 — or the same or different plurality is mentioned, the same or 1 to different 3 is specifically mentioned, and the same or 1 to different 2 is desirable. As an alkoxy group in R1, the straight chain or branching alkoxy group of carbon numbers 1-6 is mentioned, for example, and, specifically, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, 1, and 1-dimethylethoxy, pentoxy, HEKISOKISHI, etc. are mentioned. As a substituent in the permutation alkoxy group of R1, the alkoxy group (for example, the straight chain or branching alkoxy group of carbon numbers 1-6 is mentioned, and, specifically, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, 1, and 1-dimethylethoxy, pentoxy, HEKISOKISHI, etc. are mentioned.) of a halogen atom (for example, a fluorine, chlorine, a bromine, iodine, etc. are mentioned.) and carbon numbers 1-6 etc. is mentioned, for example. As an alkyl sulfonyl group in R1, the alkyl sulfonyl group of carbon numbers 1-6 is mentioned, for example, and a methyl sulfonyl, an ethyl sulfonyl, a propyl sulfonyl, a butyl sulfonyl, a pentyl sulfonyl, a hexyl sulfonyl, etc. are specifically mentioned.
[0010] As an aryloxy group in R1, the aryloxy group of carbon numbers 6-10 is mentioned, and, specifically, a phenyloxy radical etc. is mentioned. As a substituent in the permutation aryloxy group of R1 For example, a hydroxyl group, a halogen atom (for example, a fluorine, chlorine, a bromine, iodine, etc. are mentioned.) The alkoxy group of carbon numbers 1-6 (for example, the straight chain or branching alkoxy group of carbon numbers 1-6 is mentioned specifically) For example, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, The alkoxy group permuted by halogen atoms, such as 1 and 1-dimethylethoxy, pentoxy, and HEKISOKISHI, (for example, trifluoro methoxy, 1 and 1, 1-trifluoroethoxy, pentafluoro ethoxy ** TORIKURORO methoxy, etc. are mentioned.) It is mentioned. Moreover, an adjoining alkoxy group may join together, for example, a methylene dioxy radical and an ethylene dioxy radical may be formed. An alkyl sulfonyl group (for example, the alkyl sulfonyl group of carbon numbers 1-6 is mentioned, and a methyl sulfonyl, an ethyl sulfonyl, a propyl sulfonyl, a butyl sulfonyl, a pentyl sulfonyl, a hexyl sulfonyl, etc. are specifically mentioned.) etc. is mentioned. as the number of the substituents in the permutation aryloxy group of R1 — 1 — or the same or different plurality is mentioned, the same or 1 to different 3 is specifically mentioned, and the same or 1 to different 2 is desirable. As a heteroaryloxy radical in R1, the heteroaryloxy radical which has 1 to 2 is mentioned in a nitrogen atom, and, specifically, a pyridyloxy radical, a pyrimidyl oxy-radical, etc. are mentioned. As a substituent in the permutation heteroaryloxy radical of R1 For example, a hydroxyl group, a halogen atom (for example, a fluorine, chlorine, a bromine, iodine, etc. are mentioned.) The alkoxy group of carbon numbers 1-6 (for example, the straight chain or branching alkoxy group of carbon numbers 1-6 is mentioned, and, specifically, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, 1, and 1-dimethylethoxy, pentoxy, HEKISOKISHI, etc. are mentioned.) The alkoxy group (for example, trifluoro methoxy, 1 and 1, 1-trifluoroethoxy, pentafluoro ethoxy ** TORIKURORO methoxy, etc. are mentioned.) permuted by the halogen atom is mentioned. as the number of the substituents in the permutation heteroaryloxy radical of R1 — 1 — or the same or different plurality is mentioned, the same or 1 to different 3 is specifically mentioned, and the same or 1 to different 2 is desirable.
[0011] As an alkyloxy carbonyl group in R2, the alkyloxy carbonyl group of carbon numbers 2-7 is mentioned, for example, and, specifically, methyloxy carbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. As an alkyl group in the permutation alkyl of R2, the straight chain or branching alkyl group of carbon numbers 1-6 is mentioned, and, specifically, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 3-methylpropyl, 1, and 1-dimethyl ethyl, pentyl, hexyl, etc. are mentioned. as the substituent in the permutation alkyl group of R2 — an alkyloxy carbonyl group (for example, the alkyloxy carbonyl group of carbon numbers 2-7 is mentioned, and, specifically, methyloxy carbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned.) — further — a maleic anhydride, a methyl maleic anhydride, etc. — etc. — it is mentioned. As a carbamoyl group by which R2 may be permuted Alkyl carbamoyl group (for example, the alkyl carbamoyl group of carbon numbers 1-6 is mentioned) Specifically Methyl carbamoyl, ethyl carbamoyl, propyl carbamoyl, 2-propyl carbamoyl, butylcarbamoyl,

2-butylcarbamoyl, 3-methylpropyl carbamoyl, 1, and 1-dimethyl ethyl carbamoyl, pentyl carbamoyl, hexyl carbamoyl, etc. are mentioned. Dialkyl carbamoyl group (for example, as a dialkyl carbamoyl group of carbon numbers 2-12) for example, dimethyl carbamoyl, diethylcarbamoyl, ethyl methyl carbamoyl, dipropyl carbamoyl, dibutyl carbamoyl, etc. are mentioned. It is mentioned.

[0012] As an annular carbamoyl group by which R2 may be permuted, a cycloalkyl carbamoyl group (for example, the cycloalkyl carbamoyl group of carbon numbers 3-7 is mentioned, for example, cyclo propyl carbamoyl, cyclo butylcarbamoyl, cyclopentyl carbamoyl, cyclohexyl carbamoyl, etc. are mentioned.) is mentioned. As a substituent of the permutation alkyl carbamoyl group in R2, a hydroxyl group, a carboxy group, a halogen atom (for example, a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom are mentioned.), etc. are mentioned. As a substituent of a permutation dialkyl carbamoyl group, a hydroxyl group, a carboxy group, a halogen atom (for example, a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom are mentioned.), heterocycle (for example, 0 to 1 or oxygen atom **** heterocycle is mentioned [atom / nitrogen] in 1 to 2 and an oxygen atom, and, specifically, pyrrolidine, pyrrolidone, piperidine, imidazole, morpholine, and furan ** is mentioned.), etc. are mentioned. As a substituent of the permutation cycloalkyl carbamoyl group in R2, a hydroxyl group, a carboxy group, a halogen atom (for example, a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom are mentioned.), etc. are mentioned. as the number of the substituents in the permutation carbamoyl group of R2, a permutation alkyl carbamoyl group, and a permutation cycloalkyl carbamoyl group -- 1 -- or the same or different plurality is mentioned, the same or 1 to different 3 is specifically mentioned, and the same or 1 to different 2 is desirable.

[0013] As an alkyloxy carbonyl group in R3, the alkyloxy carbonyl group of carbon numbers 2-7 is mentioned, for example, and, specifically, methyloxy carbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. As an alkyl group in the permutation alkyl of R3, the straight chain or branching alkyl group of carbon numbers 1-6 is mentioned, and, specifically, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 3-methylpropyl, 1, and 1-dimethyl ethyl, pentyl, hexyl, etc. are mentioned. as the substituent in the permutation alkyl group of R3 -- an alkyloxy carbonyl group (for example, the alkyloxy carbonyl group of carbon numbers 2-7 is mentioned, and, specifically, methyloxy carbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned.) -- a maleic anhydride, a methyl maleic anhydride, etc. are mentioned further. However, R2 and R3 do not become a hydrogen atom at coincidence. As heterocycle which R2 and R3 combine and form, iso oxazolidine -3, 5-dione, 4, and 4-dimethyl iso oxazolidine -3, 5-dione, etc. are mentioned, for example.

[0014] As an alkyl group of the permutation alkyl group in R4, the straight chain or branching alkyl group of carbon numbers 1-6 is mentioned, and, specifically, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 3-methylpropyl, 1, and 1-dimethyl ethyl, pentyl, hexyl, etc. are mentioned. As a substituent in the permutation alkyl group of R4, a hydroxyl group, the amino group, a guanidino radical, a carboxy group, a halogen atom, etc. are mentioned. as the number of the substituents in the permutation alkyl group of R4 -- 1 -- or the same or different plurality is mentioned, the same or 1 to different 3 is specifically mentioned, and the same or 1 to different 2 is desirable. As an alkyl sulfonyl group in R4, the alkyl sulfonyl group of carbon numbers 1-6 is mentioned, for example, and a methyl sulfonyl, an ethyl sulfonyl, a propyl sulfonyl, a butyl sulfonyl, a pentyl sulfonyl, a hexyl sulfonyl, etc. are specifically mentioned. As a permutation carbamoyl group in R4, an alkyl carbamoyl group for example, the alkyl carbamoyl group of carbon numbers 1-6 mentions -- having -- concrete -- methyl carbamoyl -- ethyl carbamoyl, propyl carbamoyl, 2-propyl carbamoyl, butylcarbamoyl, 2-butylcarbamoyl, 3-methylpropyl carbamoyl, 1, and 1-dimethyl ethyl carbamoyl, pentyl carbamoyl, hexyl carbamoyl, etc. are mentioned. Cycloalkyl carbamoyl group (for example, the cycloalkyl carbamoyl group of carbon numbers 3-7 is mentioned) cyclo propyl carbamoyl, cyclo butylcarbamoyl, cyclopentyl carbamoyl, cyclohexyl carbamoyl, etc. are mentioned. Permutation alkyl carbamoyl group (as an alkyl carbamoyl group part) The alkyl carbamoyl group of carbon numbers 1-6 is mentioned. Specifically For example, methyl carbamoyl, Ethyl carbamoyl, propyl carbamoyl, 2-propyl carbamoyl, butylcarbamoyl, 2-butylcarbamoyl, 3-methylpropyl carbamoyl, 1, and 1-dimethyl ethyl carbamoyl, pentyl carbamoyl, hexyl carbamoyl, etc. are mentioned. As a substituent, a hydroxyl group, a carboxy group, a halogen atom (for example, a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom are mentioned.), heterocycle (for example, 0 to 1 or oxygen atom **** heterocycle is mentioned [atom / nitrogen] in 1 to 2 and an oxygen atom, and, specifically, pyrrolidine, pyrrolidone, piperidine, imidazole, morpholine, and furan ** is mentioned.), etc. are mentioned.

[0015] as the number of the substituents in the permutation carbamoyl group of R4 -- 1 -- or the same or different plurality is mentioned, the same or 1 to different 3 is specifically mentioned, and the same or 1 to different 2 is desirable. As an alkyloxy carbonyl group in R4, the alkyloxy carbonyl group of carbon numbers 2-7 is mentioned, for example, and, specifically, methyloxy carbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. As a substituent in the permutation alkyloxy carbonyl group of R4, cycloalkyloxy carbonyloxy group (for example, the cycloalkyloxy carbonyloxy group of carbon numbers 4-8 is mentioned, and, specifically, cyclopropyloxy carbonyloxy, cyclobutyloxy carbonyloxy, cyclopenthyloxycarbonyloxy, cyclohexyloxy carbonyloxy, etc. are mentioned.) etc. is mentioned.

[0016] As an alkyl group of the permutation alkyl group in R5, the straight chain or branching alkyl group of carbon numbers 1-6 is mentioned, and, specifically, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 3-methylpropyl, 1, and 1-dimethyl ethyl, pentyl, hexyl, etc. are mentioned. As a substituent in the permutation alkyl group of R5, a hydroxyl group, the amino group, a guanidino radical, a carboxy group, a halogen atom, etc. are mentioned. as the number of the substituents in the permutation alkyl group of R5 -- 1 -- or the same or different plurality is mentioned, the same or 1 to different 3 is specifically mentioned, and the same or 1 to different 2 is desirable. As an alkyl sulfonyl

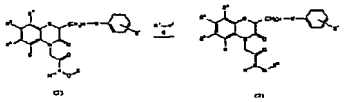
group in R5, the alkyl sulfonyl group of carbon numbers 1-6 is mentioned, for example, and a methyl sulfonyl, an ethyl sulfonyl, a propyl sulfonyl, a butyl sulfonyl, a pentyl sulfonyl, a hexyl sulfonyl, etc. are specifically mentioned. As a permutation carbamoyl group in R5, an alkyl carbamoyl group for example, the alkyl carbamoyl group of carbon numbers 1-6 mentions — having — concrete — methyl carbamoyl — ethyl carbamoyl, propyl carbamoyl, 2-propyl carbamoyl, butylcarbamoyl, 2-butylcarbamoyl, 3-methylpropyl carbamoyl, 1, and 1-dimethyl ethyl carbamoyl, pentyl carbamoyl, hexyl carbamoyl, etc. are mentioned. Dialkyl carbamoyl group (for example, as a dialkyl carbamoyl group of carbon numbers 2-12) for example, dimethyl carbamoyl, diethylcarbamoyl, ethyl methyl carbamoyl, dipropyl carbamoyl, dibutyl carbamoyl, etc. are mentioned. Cycloalkyl carbamoyl group (for example, the cycloalkyl carbamoyl group of carbon numbers 3-7 is mentioned, for example, cyclo propyl carbamoyl, cyclo butylcarbamoyl, cyclopentyl carbamoyl, cyclohexyl carbamoyl, etc. are mentioned.) Permutation alkyl carbamoyl group (as an alkyl carbamoyl group part) The alkyl carbamoyl group of carbon numbers 1-6 is mentioned. Specifically For example, methyl carbamoyl, Ethyl carbamoyl, propyl carbamoyl, 2-propyl carbamoyl, butylcarbamoyl, 2-butylcarbamoyl, 3-methylpropyl carbamoyl, 1, and 1-dimethyl ethyl carbamoyl, pentyl carbamoyl, hexyl carbamoyl, etc. are mentioned. As a substituent, they are a hydroxyl group, a carboxy group, a halogen atom (for example, a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom are mentioned.), and a permutation dialkyl carbamoyl group (as a dialkyl carbamoyl group part, dimethyl carbamoyl, diethylcarbamoyl, ethyl methyl carbamoyl, dipropyl carbamoyl, dibutyl carbamoyl, etc. are mentioned, for example, for example as a dialkyl carbamoyl group of carbon numbers 2-12.). As a substituent, a hydroxyl group, a carboxy group, halogen atom (for example, fluorine atom, chlorine atom, bromine atom, and iodine atom are mentioned.) heterocycle (for example, 0 to 1 or oxygen atom **** heterocycle is mentioned [atom / nitrogen] in 1 to 2 and an oxygen atom, and, specifically, pyrrolidine, pyrrolidone, piperidine, imidazole, morpholine, and furan ** is mentioned.), etc. are mentioned.

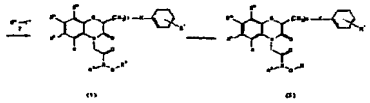
[0017] as the number of the substituents in the permutation carbamoyl group and permutation alkyl carbamoyl group of R5 — 1 — or the same or different plurality is mentioned, the same or 1 to different 3 is specifically mentioned, and the same or 1 to different 2 is desirable. As an alkyloxy carbonyl group in R5, the alkyloxy carbonyl group of carbon numbers 2-7 is mentioned, for example, and, specifically, methyloxy carbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. As an annular carbamoyl group in R5, it is a dialkyl carbamoyl group (as a dialkyl carbamoyl group part), for example. for example, as a dialkyl carbamoyl group of carbon numbers 2-12 For example, dimethyl carbamoyl, diethylcarbamoyl, ethyl methyl carbamoyl, The radical combined through association or a hetero atom (a nitrogen atom or oxygen atom) is mentioned. dipropyl carbamoyl, dibutyl carbamoyl, etc. mention — having — specifically N-pyrrolidinyl carbonyl, N-piperidinyl carbonyl, N-mol HORINIRU carbonyl, N-PIRARIJI nil carbonyl **********. As a substituent of the annular carbamoyl group of R5, an alkanoyl radical (for example, the alkanoyl radical of carbon numbers 2-6 is mentioned, and, specifically, acetyl, the propanoyl butanoyl, hepta-noil, hexa noil, etc. are mentioned.) etc. is mentioned. As an alkyloxy carbonyl group in R5, the alkyloxy carbonyl group of carbon numbers 2-7 is mentioned, for example, and, specifically, methyloxy carbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. As a substituent in the permutation alkyloxy carbonyl group of R5, cycloalkyloxy carbonyloxy group (for example, the cycloalkyloxy carbonyloxy group of carbon numbers 4-8 is mentioned, and, specifically, cyclopropyloxy carbonyloxy, cyclobutyloxy carbonyloxy, cyclopenthyloxycarbonyloxy, cyclohexyloxy carbonyloxy, etc. are mentioned.) etc. is mentioned.

[0018] As an alkyloxy carbonyl group in R6, the alkyloxy carbonyl group of carbon numbers 2-7 is mentioned, for example, and, specifically, methyloxy carbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. As a substituent in the permutation alkyloxy carbonyl group of R6, cycloalkyloxy carbonyloxy group (for example, the cycloalkyloxy carbonyloxy group of carbon numbers 4-8 is mentioned, and, specifically, cyclopropyloxy carbonyloxy, cyclobutyloxy carbonyloxy, cyclopenthyloxycarbonyloxy, cyclohexyloxy carbonyloxy, etc. are mentioned.) etc. is mentioned.

[0019] The 2nd mode of this invention is related with the matrix METARO protease activity inhibitor which makes this invention compound an active principle. this invention compound is metabolized in the living body, and shows the effective matrix METARO protease inhibition activity as hydroxamic acid. And since oral absorbency is high, it is useful also as a prodrug and is a matrix METARO protease activity inhibitor useful as an oral absorption agent. The matrix METARO protease activity inhibitor of this invention shows remarkable inhibitory action to MMP-13 or MMP-3 especially. [0020] The 3rd mode of this invention is related with articular disease therapy agents, such as deformation arthrosis which makes this invention compound an active principle, and rheumatoid arthritis, a cancer transition inhibitor or an anti-inflammation therapy agent, and a periodontitis therapy agent. Since this invention compound shows remarkable inhibitory action to MMP-13 or MMP-3 especially, it can use it as a therapy agent of diseases, such as articular disease therapy agents, such as deformation arthrosis and rheumatoid arthritis, or gum disease.

[0021] The heterocyclic compound which is the medicinal active principle of this invention can be made into the salt permitted on pharmaceutical sciences. As a salt permitted on pharmaceutical sciences, an acid addition salt and a base addition salt are mentioned. As an acid addition salt, organic-acid salts, such as inorganic-acid salts, such as a hydrochloride, hydrobromate, and a sulfate, citrate, an oxalate, apple acid chloride, a tartrate, fumarate, and a maleate, are mentioned, for example, and organic base salts, such as inorganic base salts, such as sodium salt and a calcium salt, a meglumine salt, and a tris hydroxymethyl aminomethane salt, are mentioned as a base addition salt. Moreover, solvates, such as a hydrate of the salt permitted on a benzothiazin-3-ON derivative or its pharmaceutical sciences, are also included in this invention.

[0022] The compound of formula (3) - (5) expressed with the formula (1) of this invention can be manufactured by the following approaches and the approach according to it.
[Formula 3]


[Formula 4]


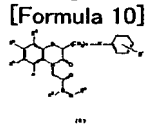
the inside Z of [type — hydrogen or an alkali-metal atom — expressing — R2 and R3 — formula: — [Formula 5]


(— the inside R9 of a formula expresses the alkyl group which may be permuted, or the amino group which may be permuted.) — the alkyl group which may be permuted is expressed. R7 and R8 — formula: — [Formula 6]


(— the inside R10 of a formula expresses the alkyl group which may be permuted.) — the alkyl group which may be permuted, or the amino group which may be permuted is expressed. Y1 and Y2 express a hydrogen atom, a hydroxyl group, a chlorine atom, a bromine atom, or an iodine atom.] the reaction of the compound of a formula 2, and the compound of a formula 6 — R2 — formula: — [Formula 7]


(— R10 is synonymous with the above among a formula.) — R7 [in / when expressed / a formula 6] — formula: — [Formula 8]


(— R10 is synonymous with the above among a formula.) — Y1 can carry out to peptide chemistry according to a well-known approach ("the foundation of peptide synthesis and experiment" Izumi store Nobuo et al., Maruzen, etc.) using the compound which is a hydroxyl group, a chlorine atom, a bromine atom, or an iodine atom. For example, the C edge activating method, the approach (approach using DCC (N and N'-dicyclohexylcarbodiimide) etc.) using coupling reagents (an acid halide method, an acid azide method, a mixed acid anhydride method, the activity ester method, symmetry acid anhydride, etc.), the N edge activating methods (HOSUFAZO the isocyanate method, law, a phosphite method, etc.), etc. are mentioned. As an approach using a coupling reagent, it is an N-(dimethylaminoethyl)-N'-ethyl carbodiimide in N.N-dimethylformamide (DMF) about the compound of a formula 2, and the compound of a formula 6, for example. The approach of being 0 degree C - a room temperature under a hydrochloride (WSC hydrochloride) and 1-hydroxy benzotriazol (HOBt) existence, and condensing etc. is mentioned. Although it can obtain by making it react at a room temperature the bottom of the nucleophilic substitution usually used using the alkyl group by which R7 in a formula 6 may be permuted, and the compound whose Y1 is a chlorine atom, a bromine atom, or an iodine atom, for example, potassium carbonate, and base existence like DBU, and among DMF when it is the alkyl group by which R2 may be permuted, alkali metal like sodium is suitable for Z of the compound of a formula 2. R2 — formula: — [Formula 9]

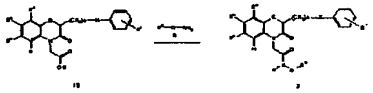

[— the inside R9 of a formula expresses the amino group which may be permuted.] It can obtain by making it react at a room temperature a ** case the bottom of coexistence of the urethane formation reaction for which it is usually used using the amino group by which R7 in a formula 6 may be permuted, and the compound whose Y1 is a hydrogen atom, for example, carbonyldiimidazole, a phosgene, etc., and among THF. Moreover, the formula 8 [0023]
[Formula 10]


[— R4-R6, and X and n are synonymous with the above among [R1-R2] a formula.] It can come out and the compound expressed can also be compounded by the single step to the compound of a formula 2 by the above-mentioned approach using the compound of the formula 6 of an excessive amount, and other reaction reagents. Moreover, it is a formula [** 11] to the compound of a formula 2.


[— Q expresses among a formula the alkylene which may be permuted and Y1 and Y2 are synonymous with the above.] A compound including heterocycle is compoundable by coming out and using the compound expressed on

the above and these conditions. Moreover, the compound of a formula 3 can also be manufactured by the bottom type.

[Formula 12]



[— R4-R6, and X and n are synonymous with the above among [R1-R2] a formula.] R2 among the reactions of the compound of the formula 2 of the above [this reaction], and the compound of a formula 6 — formula: — [Formula 13]

(— R10 is synonymous with the above among a formula.) — when expressed, it can be based on the same approach as what was used. The compound expressed with a formula 4 can be obtained from the compound of a formula 3, and the compound of a formula 7 by the approach which obtained the compound of a formula 3 from the compound of a formula 2, and the same approach. moreover, the protective group of the hydroxyl group by which the compound of a formula 5 is expressed with R2 of the compound of a formula 4 — a law — it can obtain by carrying out deprotection according to a method. For example, deprotection can be carried out by processing with hydrocracking, hydrolysis, or the Lewis acid in a nonaqueous solution. For example, using hydrogenation catalysts (for example, palladium catalyst etc.) as a reaction of hydrocracking, among an inactive organic solvent (for example, a methanol, ethanol, etc.), acids, such as an acetic acid and a hydrochloric acid, can be added and it can react at a room temperature under a hydrogen ambient atmosphere if needed. As a reaction of hydrolysis, sulphur-containing compounds, such as an anisole or thioanisole, a dimethyl sulfide, and ethane dithiol, can be added among a non-solvent or a water organic solvent if needed under acid existence, such as an acetic acid, trifluoroacetic acid, methansulfonic acid, p-toluenesulfonic acid, a sulfuric acid, a hydrochloric acid, and a hydrobromic acid, and it can react at a room temperature, for example. Or it can also be based on the boron tribromide in the inside of aprotic solvents, such as a methylene chloride, boron trichloride, and an iodation trimethyl silane. However, as for the protective group expressed with R2, it is desirable to choose the protective group of the hydroxyl group expressed with R3 and the protective group from which deprotection conditions differ.

[0024] The intermediate field for manufacturing the compound or it which is contained in this invention expressed with a formula (1) can be refined by the usual approach. For example, a column chromatography, recrystallization, etc. can refine. As a recrystallization solvent, these mixed solvents [, such as a hydrocarbon system solvent,], such as ketone solvent, such as aromatic hydrocarbon system solvents, such as ester solvent, such as ether system solvents, such as alcoholic solvent, such as a methanol, ethanol, and 2-propanol, and diethylether, and ethyl acetate, and toluene, and an acetone, and a hexane, etc. are mentioned, for example. Moreover, if required in case an above-mentioned reaction is performed, the technique of protection and deprotection can be used. The technique of protection and deprotection is described in detail at (T.W.Greene and P.G.M.Wuts, "Protecting Groups in Organic Synthesis", 1991, JOHN WILEY & SONS, and INC.). The benzothiazin-3-ON derivative of this invention or its salt may form solvates, such as a hydrate, and this invention also contains these.

[0025] If the benzothiazin-3-ON derivative of this invention or its salt may have the substituent which has asymmetrical carbon and is in such a compound when dissymmetry arises or, an optical isomer exists. The mixture and the isolated thing of each of these isomers are included in this invention compound. As an approach of obtaining such an optical isomer purely, optical resolution is mentioned, for example. as an optical-resolution method — a benzothiazin-3-ON derivative or its intermediate field — the inside of an inert solvent (for example, a methanol —) Ether system solvents, such as alcoholic solvent, such as ethanol and 2-propanol, and diethylether, Aromatic hydrocarbon system solvents, such as ester solvent, such as ethyl acetate, and toluene, These mixed solvents and optical activity acids, such as an acetonitrile for example, monocarboxylic acid, such as mandelic acid, an N-benzyloxy alanine, and a lactic acid, — Sulfonic acid and salts, such as dicarboxylic acid, such as a tartaric acid, o-diisopropylidene tartaric acid, and a malic acid, camphor sulfonic acid, and BUROMO camphor sulfonic acid, can also be made to form. Moreover, when a benzothiazin-3-ON derivative or its intermediate product has acid substituents, such as a carboxyl group, optical activity amine (for example, organic amines, such as alpha-phenethylamine, kinin, quinidine, cinchonidine, cinchonine, and strychnine) and salt can also be made to form.

[0026] As temperature in which a salt is made to form, the range of the boiling point of a solvent is mentioned from a room temperature. In order to raise optical purity, it is desirable to once raise temperature to near the boiling point of a solvent. Before separating the salt which deposited, it can cool if needed, and yield can be raised. the amount of optical activity acid or amine used — a substrate — receiving — about 0.5- the range of about 2.0Eq — the range of order of 1Eq is preferably suitable. A crystal is recrystallized if needed in an inert solvent (for example, these mixed solvents, such as aromatic hydrocarbon system solvents, such as ester solvent, such as ether system solvents, such as alcoholic solvent, such as a methanol, ethanol, and 2-propanol, and diethylether, and ethyl acetate, and toluene, and an acetonitrile), and a salt [optical activity / high grade] can also be obtained. The obtained salt can be processed with an acid or a base by the usual approach if needed, and a free object can also be acquired.

[0027] The benzothiazin-3-ON derivative of this invention or its salt can be prescribed for the patient taking-orally-wise or parenterally. When prescribing a medicine for the patient in taking orally, a medicine can be prescribed for the patient with the administration gestalt usually used. Parenterally, a medicine can be prescribed for the patient in

forms, such as a partial administration agent, injections, an endermic agent, and a pernasal agent. As an oral agent or a rectum administration agent, a capsule, a tablet, a pill, powder, cachets, a suppository, liquids and solutions, etc. are mentioned, for example. As injections, a sterile solution or suspension etc. is mentioned, for example. As a partial administration agent, a cream, ointment, a lotion, an endermic agent (the usual patch agent, matrix agent), etc. are mentioned, for example. The above-mentioned dosage forms are the usual approaches, and are manufactured with the excipient and additive which are permitted pharmacologically. As the excipient permitted pharmacologically and an additive, support, a binder, perfume, a buffer, a thickener, a coloring agent, a stabilizer, an emulsifier, a dispersant, a suspending agent, antiseptics, etc. are mentioned. As support permitted pharmacologically, a magnesium carbonate, magnesium stearate, talc, sugar, a lactose, pectin, a dextrin, starch, gelatin, tragacanth, methyl cellulose, a sodium carboxymethyl cellulose, a low-melt point point wax, cocoa butter, etc. are mentioned, for example. A capsule can be manufactured by putting this invention compound into inside with the support permitted pharmacologically. It can mix with the excipient permitted pharmacologically, or the benzothiazin-3-ON derivative of this invention or its salt can be put in without an excipient into a capsule. Cachets can also be manufactured by the same approach.

[0028] A solution, suspension, an emulsion, etc. are mentioned as liquids and solutions for injection. For example, a water solution, a water-propylene glycol solution, etc. are mentioned. Liquids and solutions can also be manufactured in the form of the solution of the polyethylene glycol or/and propylene glycol which may also contain water. The suitable liquids and solutions for internal use can add this invention compound to water, and, in addition, can manufacture a coloring agent, perfume, a stabilizing agent, a sweetening agent, a resolvent, a thickener, etc. if needed. Moreover, the suitable liquids and solutions for internal use add the benzothiazin-3-ON derivative of this invention, or its salt to water with a dispersant, and can manufacture it also by making it ****. The nature pharmacologically permitted as a thickener, for example or synthetic gum, resin, methyl cellulose, a sodium carboxymethyl cellulose, or a well-known suspending agent is mentioned.

[0029] As a partial administration agent, the above-mentioned liquids and solutions and a cream, aerosol, a spray, powder material, a lotion, ointment, etc. are mentioned. The above-mentioned partial administration agent is mixed with the diluent and support which are used for the benzothiazin-3-ON derivative of this invention, or usual [its / salt and usual] and which are permitted pharmacologically, and can be manufactured. Ointment and a cream add a thickener and/or a gelling agent to aquosity or an oily basis, pharmaceutical-preparation-ize, and are obtained. As this basis, water, liquid paraffin, vegetable oil (peanut oil, castor oil, etc.), etc. are mentioned, for example. As a thickener, software paraffin, aluminum stearate, the cetostearyl alcohol, propylene glycol, a polyethylene glycol, lanolin, hydrogenation lanolin, beeswax, etc. are mentioned, for example. A lotion can add one kind or the stabilizer beyond it permitted pharmacologically, a suspending agent, an emulsifier, a dispersing agent, a thickener, a coloring agent, perfume, etc. to a water or oily basis.

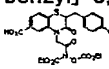
[0030] Powder is pharmaceutical-preparation-ized with the basis of the powder permitted pharmacologically. Talc, a lactose, starch, etc. are mentioned as a basis. A drop can carry out [****]-izing with the basis of aquosity or nonaqueous nature, a kind or the dispersing agent beyond it permitted pharmacologically, a suspending agent, a resolvent, etc. A partial administration agent may also contain antiseptics, such as hydroxybenzoic-acid methyl, hydroxybenzoic-acid propyl, chlorocresol, and benzalkonium chloride, and a bacteria growth inhibitor if needed. The pharmaceutical preparation which made the benzothiazin-3-ON derivative of this invention or its salt the liquids-and-solutions spray, the powder, or the drop made into an active principle can be prescribed for the patient in pernasality. the case where it administers orally although a dose and the count of administration change with a symptom, age, weight, administration gestalten, etc. — usually — an adult — receiving — per day — about 1- the range of about 500mg — desirable — about 5- the range of about 100mg can be prescribed for the patient in 1 time or several steps. the case where a medicine is prescribed for the patient as injections — about 0.1- the range of about 300mg — desirable — about 1- the range of about 100mg can be prescribed for the patient in 1 time or several steps.

[0031]

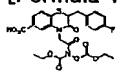
[Translation done.]

EXAMPLE

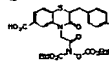
[Example] Although an example explains this invention concretely below, this invention is not limited at all by these examples.
Example 14-(2-[(ethoxycarbonyl) [(ethoxycarbonyl) oxy-] amino]-2-oxo-ethyl)-3-oxy--2-[4-(trifluoro methoxy) benzyl]-3, 4-dihydro-2H-1, a 4-benzothiazin-6-carboxylic acid. [Formula 14]



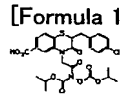
5%-ethane dithiol content TFA (2ml) was added to 4-(2-[(ethoxycarbonyl) [(ethoxycarbonyl) oxy-] amino]-2-oxo-ethyl)-3-oxy--2-[4-(trifluoro methoxy) benzyl]-3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic-acid t-butyl ester (520mg, 0.79mmol), and it put at the room temperature for 3 hours. 375mg of 4-(2-[(ethoxycarbonyl) [(ethoxycarbonyl) oxy-] amino]-2-oxo-ethyl)-3-oxy--2-[4-(trifluoro methoxy) benzyl]-3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acids was obtained by adding and carrying out vacuum concentration of the toluene, and refining residue with a silica gel column chromatography (chloroform: acetic-acid =100:1). 1 H-NMR(DMSO-d6, deltappm): 1.22-1.36 (6H, m), 2.80 (1H, m) 3.14 (1H, m) 4.09 (1H, br-s), 4.31-4.43 (4H, m) 4.62 (0.1H, d, J=20Hz), 4.76 (0.1H, d, J=20Hz) 5.00-5.49 (1.8H, m), 7.26 (2H, br-s) 7.35 (2H, br-d, J=8.0Hz) 7.51-7.59 (2H, m) 7.64 (1H, dd, J=1.2Hz, 9.2Hz) 13.2 (1H, br-s)
[0032] Example 24- (2-[(ethoxycarbonyl) [(ethoxycarbonyl) oxy-] Amino]-2-oxo-ethyl)-2-(4-fluoro benzyl)-3-oxy-- by the approach of a publication, and the similar approach in the 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic-acid example 1 4-(2-[(ethoxycarbonyl) [(ethoxycarbonyl) oxy-] amino]-2-oxo-ethyl)-2-(4-fluoro benzyl)-3-oxy-- The 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid was obtained.
[Formula 15]



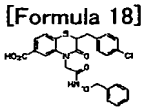
1 H-NMR(DMSO-d6, deltappm): 1.27 (6H, m), 2.75 (1H, m) 3.14 (1H, br-s), 4.02 (1H, br-s) 4.34-4.42 (4H, m), 5.11-5.49 (2H, m) 7.09 (2H, br-s), 7.23 (2H, br-s) 7.53 (1H, d, J=8.0Hz) 7.57 (1H, br-s) 7.64 (1H, dd, J=1.4Hz, 8.0Hz) 13.2 (1H, br-s)
[0033] Example 34-[2- () [[] (Benzyl) by the approach similar to the carbonyl] {[(benzyl) carbonyl] oxy-} amino-2-oxo-ethyl]-3-oxy--2-[4-(trifluoro methoxy) benzyl]-3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic-acid example 1 The 4-[2-([(benzyl) carbonyl [[(benzyl) carbonyl] oxy-]] amino)-2-oxo-ethyl]-3-oxy--2-[4-(trifluoro methoxy) benzyl]-3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid was obtained.
[Formula 16]

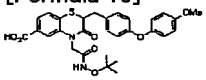


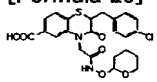
1 H-NMR(DMSO-d6, deltappm): 2.84 (1H, br-s), 3.19 (1H, br-s) 4.07 (1H, br-s), 5.33-5.51 (4H, m) 7.24 (2H, br-s), 7.31-7.40 (12H, m) 7.53 (1H, d, J=8.0Hz) 7.59 (1H, br-s) 7.63 (1H, d, J=8.0Hz)
[0034] Example 42- (4-chloro benzyl)-4-(2-[(i-propoxy carbonyl) [(i-propoxy carbonyl) oxy-] amino]-2-oxo-ethyl)-3-oxy-- by the approach similar to the 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic-acid example 1 2-(4-chloro benzyl)-4-(2-[(i-propoxy carbonyl) [(i-propoxy carbonyl) oxy-] amino]-2-oxo-ethyl)-3-oxy-- The 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid was obtained.
[0035]
[Formula 17]

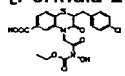


1 H-NMR(DMSO-d6, deltappm): 1.27-1.38 (12H, m), 2.75 (1H, dd, J=9.4Hz, 14.0Hz), 3.14 (1H, m) 4.05 (1H, m) 4.95 (1H, m), 5.10 (1H, m) 5.05-5.50 (2H, m), 7.23 (2H, d, J=8Hz) 7.32 (2H, bs) 7.51 (2H, m) 7.63 (1H, d, J=8.4Hz) 13.19 (1H, bs)
[0036] an example 5-3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic-acid 4-[2-[(benzyl) amino]-2-oxo-ethyl]-2-(4-chloro benzyl)-3-oxy-[0037 --]

[Formula 18]


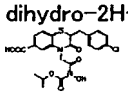
The [6-(t-butoxycarbonyl)-2-(4-chloro benzyl)-3-oxy--2, 3-dihydro-4H-1, and 4-benzothiazin-4-IRU] acetic acid (500mg) was melted to THF (3ml), N-methyl morpholine (130microl) and chloro formic acid isobutyl (152microl) were added at 0 degree C, and it stirred for 5 minutes. Subsequently, DMF (3ml), O-benzyl hydroxylamine hydrochloride (215mg), and N-methyl morpholine (148microl) were added, and it stirred at the room temperature for 30 minutes by 0 degree C for 15 hours. 1N After adding HCl (3ml) and stirring for 15 minutes, the reaction mixture was diluted with water. After ethyl acetate extracted this, saturation brine washed the organic layer. The organic layer was dried with sulfuric anhydride magnesium, and the drying agent was carried out the ** exception and carried out vacuum concentration. The silica gel column (50g, a solvent: silica gel : KISAN: ethyl acetate = 4:1, subsequently 3:1) refined the residue, and oily matter was obtained. This is melted to a methylene chloride (5ml), and they are the bottom of 0 degree C, an anisole (2ml), and TFA (5ml). In addition, it stirred at the room temperature at 4:00. The colorless crystal obtained after repeating twice the actuation which adds and carries out vacuum concentration of the toluene to a reaction mixture is ****(ed) by the ether-hexane, and it is 4-[2-[(benzyl) amino]-2-oxo-ethyl]-2-(4-chloro benzyl)-3-oxy-. - The 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid (380mg) was obtained. 1 H-NMR (DMSO-d6, deltappm): 2.76 (1H, dd, J=8.8, 13.9Hz), 3.15 (1H, dd, J=6.4, 14.0Hz), 4.01 (1H, m) 4.40-5.10 (4H, m), 7.23-7.47 (9H, m) 7.51 (1H, d, J=8.0Hz), 7.62 (1H, d, J=8.0Hz) 7.68 (1H, s) 11.11 and 11.53 (1H, each s) 13.21 (1H, br-s)
[0038] Example 64-[2-(t-butoxy amino)-2-oxo-ethyl]-2-[4-(4-methoxy phenoxy) benzyl]-3-oxy— by the approach similar to the 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic-acid example 5 4-[2-(T-butoxy amino)-2-oxo-ethyl]-2-[4-(4-methoxy phenoxy) benzyl]-3-oxy— The 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid was obtained.
[Formula 19]


1 H-NMR(DMSO-d6, deltappm): 1.16 and 1.27 (9H, each s), 2.72 (1H, m), 3.09 (1H, m), 3.74 (3H, s), 3.93 (1H, m) 4.51 (1H, d, J= 16Hz), 4.62 (1H, d, J= 16Hz) 6.78 (2H, d, J= 8Hz), 6.96 (4H, m), 7.17 (2H, d, J= 8Hz), 7.49 (1H, d, J= 8Hz), 7.60 (1H, dd, J= 1.6, 8Hz), 7.64 (1H, s), 10.54 and 10.80 (1H, each s) 13.13 (1H, br-s)
[0039] By the approach similar to the example 72-(4-chloro benzyl)-3-oxy—4-[2-oxy—2-[(tetrahydro-2H-pyran-2-yloxy) amino] ethyl]-3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic-acid example 5 The 2-(4-chloro benzyl)-3-oxy—4-[2-oxy—2-[(tetrahydro-2H-pyran-2-yloxy) amino] ethyl]-3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid was obtained.
[Formula 20]


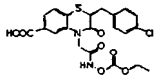
1 H-NMR (DMSO-d6, deltappm) : 1.53-1.67 (6H, m), 2.74 (1H, m) 3.13 (1H, m) 3.54 (1H, m), 3.93 (2H, m) 4.42-4.86 (3H, m), 7.25 (2H, m) 7.32 (2H, m) 7.41 (1H, d, J=7.89Hz) 7.61-7.66 (2H, m) 11.51 (1H, br-s)
[0040] Example 82-(4-chloro benzyl)-4-[2-[(ethoxycarbonyl) (hydroxy) amino]-2-oxo-ethyl]-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid [0041]
[Formula 21]


By the approach similar to an example 5 Obtained 2- (4-chloro benzyl)-3-oxy—4-[2-oxy—2-[(tetrahydro-2H-pyran-2-yloxy) amino] ethyl]-3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid Dichloromethane of t-butyl (547mg) (10ml) Bottom Nof ice-cooling-ethyl diisopropylamine (345microl) and chloro formic acid ethyl (153microl) were dropped to the solution. The temperature up was carried out to the 1 hour after room temperature, and it stirred all night. The reaction solvent was diluted with ethyl acetate after reduced pressure distilling off, water and saturation brine washed, and it dried with anhydrous sodium sulfate. The drying agent was filtered and removed, reduced pressure distilling off of the solvent was carried out, and 629mg of rough products was obtained. Then, the rough product (629mg) was dissolved in the anisole (2ml), and the bottom trifluoroacetic acid (5ml) of ice-cooling was dropped. The temperature up was carried out to the after [10 minutes] room temperature, and it stirred for 2 hours. After reaction termination, toluene (30ml) was added and reduced pressure distilling off of the solvent was carried out. The actuation which furthermore adds toluene (30ml) and carries out reduced pressure distilling off was repeated 3 more times. residue was refined by crystallization (diethylether/hexane: 1/3), and the 2-(4-chloro benzyl)-4-[2-[(ethoxycarbonyl) (hydroxy) amino]-2-oxo-ethyl]-3-oxy—3 of white solid-state, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid (368mg) was obtained.
1 H-NMR (DMSO-d6, deltappm) : 1.25 (3H, t, J=7Hz), 2.75 (1H, m) 3.14 (1H, m) 4.00 (1H, m), 4.25 (2H, q, J=7Hz) 4.67 (2H, m), 7.23 (2H, d, J=8.43Hz) 7.31 (2H, d, J=8.04Hz) 7.50 (1H, d, J=7.86Hz) 7.60-7.65 (2H, m)

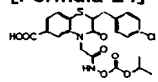
[0042] Example 92-(4-chloro benzyl)-4-[2-[hydroxy (i-propoxy carbonyl) amino]-2-oxo-ethyl]-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid [** 22]



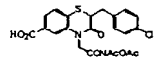
the 2-(4-chloro benzyl)-4-[2-[hydroxy (i-propoxy carbonyl) amino]-2-oxo-ethyl]-3-oxy—3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid was obtained by the approach similar to an example 8.
1 H-NMR (DMSO-d6, deltappm) : 1.28 (6H, t, J=6.21Hz), 2.76 (1H, m) 3.16 (1H, m) 4.01 (1H, m), 4.68 (2H, m) 4.87 (1H, m) 7.24 (2H, d, J=8.43Hz), 7.32 (2H, d, J= 8.22Hz) 7.52 (1H, d, J=8.07Hz) 7.61-7.66 (2H, m)
[0043] Example 102-(4-chloro benzyl)-4-(2-[[(ethoxycarbonyl) oxy-] amino]-2-oxo-ethyl)-3-oxy-- 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid [0044]
[Formula 23]



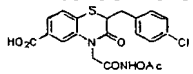
4-[2-[[(Allyloxy) Carbonyl] (hydroxy) amino]-2-oxo-ethyl]-2-(4-chloro benzyl)-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid The dichloromethane (10ml) of an allyl compound (500mg) Bottom Nof ice-cooling-ethyl diisopropylamine (325microl) and chloro formic acid ethyl (143microl) were dropped to solution. The temperature up was carried out to the 1 hour after room temperature, and it stirred all night. The reaction solvent was diluted with ethyl acetate after reduced pressure distilling off, water and saturation brine washed, and it dried with anhydrous sodium sulfate. The drying agent was filtered and removed, reduced pressure distilling off of the solvent was carried out, and the rough product was obtained. Then, the rough product was dissolved in the tetrahydrofuran (10ml), and under nitrogen-gas-atmosphere mind, formic acid (1.06ml) and tetrakis (triphenyl phosphine) palladium (326mg) were added, and it stirred at the room temperature all night. After carrying out reduced pressure distilling off of the solvent after reaction termination and diluting with ethyl acetate, water and saturation brine washed and it dried with anhydrous sodium sulfate. The drying agent was filtered and removed, reduced pressure distilling off of the solvent was carried out, and the rough product was obtained. A silica gel column chromatography (a methanol/chloroform: 1/20) refines residue, and it is 2-(4-chloro benzyl)-4-(2-[[(ethoxycarbonyl) oxy-] amino]-2-oxo-ethyl)-3-oxy-[of a white solid-state]. - The 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid (156mg) was obtained.
1 H-NMR (DMSO-d6, deltappm) : 1.27 (3H, t, J=7Hz), 2.73 (1H, m) 3.12 (1H, m) 3.93 (1H, m), 4.25 (2H, q, J=7Hz) 5.04 (1H, d, J=18.30Hz), 5.20 (1H, d, J=18.12Hz) 7.23 (2H, d, J=8.25Hz), 7.32 (2H, d, J=8.25Hz) 7.40 (1H, d, J=8.22Hz) 7.58-7.63 (2H, m)
[0045] Example 112-(4-chloro benzyl)-4-(2-[[(i-propoxy carbonyl) oxy-] amino]-2-oxo-ethyl)-3-oxy-- 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid [0046]
[Formula 24]



It is 2-(4-chloro benzyl)-4-(2-[[(i-propoxy carbonyl) oxy-] amino]-2-oxo-ethyl)-3-oxy-by the approach similar to an example 10. - The 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid was obtained.
1 H-NMR (DMSO-d6, deltappm) : 1.30 (6H, t, J=6.24Hz), 2.75 (1H, m) 3.12 (1H, m) 4.01 (1H, m), 4.93-5.03 (2H, m) 5.17 (1H, d, J=18.30Hz), 7.24 (2H, d, J=8.43Hz) 7.32 (2H, d, J=8.25Hz) 7.48-7.52 (2H, m) 7.62 (1H, d, J=8.07Hz) 10.63 (1H, br-s)
[0047] Example 124-[2-[acetyl (acetyloxy) amino]-2-oxo-ethyl]-2-(4-chloro benzyl)-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid [** 25]

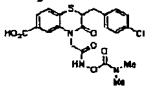


4-[2-[acetyl (acetyloxy) amino]-2-oxo-ethyl]-2-(4-chloro benzyl)-3-oxy-under nitrogen-gas-atmosphere mind - 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid t-butyl (0.4g) After adding a methyl thioether (1ml), it added triphloroacetic acid (3.5ml). Vacuum concentration was carried out 2 hours after. The silica gel column chromatography (ethyl acetate) refined residue, and it crystallized from the chloroform hexane. White 4-[2-[acetyl (acetyloxy) amino]-2-oxo-ethyl]-2-(4-chloro benzyl)-3-oxy— The 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid (57mg) was obtained.
1 H-NMR(DMSO-d6, deltappm): 2.35 and 2.36 (6H, s and br-s), 2.75 (1H, m), 3.14 (1H, m), and 4.03 (1H, m) 5.13 (2H, m) 7.23-7.25 (2H, m), 7.32-7.34 (2H, m), and 7.52- 7.54 (2H, m) and 7.63 (1H, dd, J= 1.6, 8Hz) 13.0 (1H, br-s)
[0048] Example 134-[2-[(acetyloxy) amino]-2-oxo-ethyl]-2-(4-chloro benzyl)-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid [** 26]

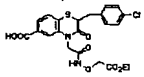


2-(4-chloro benzyl)-4-[2-(hydroxy amino)-2-oxo-ethyl]-3-oxy-under nitrogen-gas-atmosphere mind - 3, 4-

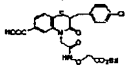
dihydro-2H-1, 4-benzothiazin-6-carboxylic acid After adding triethylamine (0.66ml) to the tetrahydrofuran (30ml) solution of t-butyl (1.1g), the acetyl chloride (0.16ml) was added under ice-cooling. It opened in saturation brine 0.5 hours after, and ethyl acetate extracted. After saturation sodium bicarbonate water washed the oil reservoir, vacuum concentration was dried and carried out with the sodium sulfate. The silica gel column chromatography refined residue. After adding a methyl thioether (1ml) to this, it added triphloroacetic acid (3ml). Vacuum concentration of the toluene was added and carried out 5 hours after. The silica gel column chromatography (ethyl acetate/hexane = 4/1) refined residue, and it crystallized from chloroform. White 4-[2-[(acetyloxy) amino]-2-oxo-ethyl]-2-(4-chloro benzyl)-3-oxy— The 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid (280mg) was obtained.
1 H-NMR(DMSO-d6, deltappm): 2.17 (3H, s), 2.75 (1H, m), 3.15 (1H, m), 4.00 (1H, m), 4.65 (1H, d, J= 16Hz) 4.72 (1H, d, J= 16Hz), 7.51 (1H, d, J= 8Hz) 7.23-7.25 (2H, m), 7.31-7.34 (2H, m), 7.62 (1H, dd, J= 1.2, 8Hz) 7.66 (1H, s) 12.18 (1H, s) 13.14 (1H, br-s)
[0049] Example 142-(4-chloro benzyl)-4-[2-([[(dimethylamino) carbonyl] oxy-} amino)-2-oxo-ethyl]-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid [** 27]



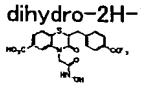
2-(4-chloro benzyl)-4-[2-(hydroxy amino)-2-oxo-ethyl]-3-oxy-under nitrogen-gas-atmosphere mind - 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid It stirred for 1 hour, after adding N and N'-carbonyldiimidazole (195mg) to the tetrahydrofuran (30ml) solution of t-butyl (0.46g) under ice-cooling. After adding a 2-N dimethylamine-tetrahydrofuran solution (1ml), it stirred at the room temperature on the 1st. It opened in saturated-ammonium-chloride water, and ethyl acetate extracted. Vacuum concentration of the oil reservoir was dried and carried out with the sodium sulfate. The silica gel column chromatography refined residue and the white solid-state (0.41g) was obtained. After adding a methyl thioether (1ml) to this, it added triphloroacetic acid (3ml). Vacuum concentration of the toluene was added and carried out 2 hours after. The silica gel column chromatography (ethyl acetate/hexane = 4/1) refined residue, and it crystallized from chloroform. White 2-(4-chloro benzyl)-4-[2-([[(dimethylamino) carbonyl] oxy-} amino)-2-oxo-ethyl]-3-oxy— The 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid (190mg) was obtained.
1 H-NMR(DMSO-d6, deltappm): 2.75 (1H, m), 2.88and(s) 2.93 (6H, each br-s) 3.15 (1H, m), 3.99 (1H, m), 4.61 (1H, d, J= 16Hz), 4.66 (1H, d, J= 16Hz), 7.50 (1H, d, J= 8.2Hz) 7.22-7.24 (2H, m), 7.31-7.33 (2H, m), 7.62 (1H, d, J= 1.6, 8Hz) 7.66 (1H, s) 12.0 (1H, br-s)
[0050] Example 152-(4-chloro benzyl)-4-[2-[(2-ethoxy-2-oxo-ethoxy) amino]-2-oxo-ethyl]-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid [** 28]



2-(4-chloro benzyl)-4-[2-[(2-ethoxy-2-oxo-ethoxy) amino]-2-oxo-ethyl]-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid t-butyl is melted to a methylene chloride (9ml). After adding an anisole (3.4ml) and TFA (9ml) in 0 degree C, it stirred at the room temperature for 5 hours. The actuation which adds and carries out vacuum concentration of the toluene to a reaction mixture was repeated twice. the obtained colorless crystal was ****(ed) by KISAN to ether -, and the 2-(4-chloro benzyl)-4-[2-[(2-ethoxy-2-oxo-ethoxy) amino]-2-oxo-ethyl]-3-oxy—3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid (320mg) was obtained.
1 H-NMR(DMSO-d6, deltappm): 1.23 (3H, t, J=7Hz), 2.76 (1H, dd, J=8.7, 13.6Hz), 3.12 (1H, dd, J=6.5, 14.0Hz), 3.99 (1H, t, J=7.3Hz) 4.18 (2H, m), 4.45-5.30 (4H, m) 7.25 (2H, d, J=8.0Hz), 7.32 (2H, d, J=7.3Hz) 7.50 (1H, d, J=7.8Hz), 7.61 (2H, m) 11.15 and 11.75 (1H, each br-s) 13.15 (1H, br-s)
[0051] Example 164-(2-[[2-(benzyl)-2-oxo-ethoxy] amino]-2-oxo-ethyl)-2-(4-chloro benzyl)-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid [** 29]

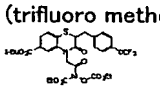


By the approach similar to an example 15, it is 4-(2-[[2-(benzyl)-2-oxo-ethoxy] amino]-2-oxo-ethyl)-2-(4-chloro benzyl)-3-oxy-. - The 3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid was obtained.
1 H-NMR(DMSO-d6, deltappm): 2.76 (1H, dd, J=8.7, 14.0Hz), 3.12 (1H, dd, J=6.7, 14.2Hz), 3.99 (1H, dd, J=6.7, 8.6Hz), 4.55 (4H, m) 5.22 (2H, s) 7.24 (2H, d, J= 8.4Hz), 7.35 (7H, m) 7.50 (1H, d, J= 8.2Hz) 7.61 (2H, m) 11.20 and 11.74 (1H, each br-s)
[0052] Example of reference 14-[2-(hydroxy amino)-2-oxo-ethyl]-3-oxy—2-[4-(trifluoro methoxy) benzyl]-3, 4-dihydro-2H-1, a 4-benzothiazin-6-carboxylic acid [** 30]

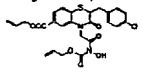


4-[2-(hydroxy amino)-2-oxo-ethyl]-3-oxy—2-[4-(trifluoro methoxy) benzyl]-3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid 5%-ethane dithiol content TFA (15ml) was added to t-butyl (1.5g, 2.93mmol), and it put at the room temperature for 3 hours. Vacuum concentration of the toluene was added and carried out, and 1.05g of 4-[2-

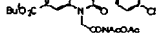
(hydroxy amino)-2-oxo-ethyl]-3-oxy—2-[4-(trifluoro methoxy) benzyl]-3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acids was obtained by ******ing residue from the mixed solvent of THF, a hexane, and the ether.
1 H-NMR(DMSO-d6, deltappm): 2.81 (1H, dd, J= 8.8, 14.5Hz), 3.20 (1H, dd, J= 6.4, 14.5Hz) 4.04 (1H, dd, J= 6.4, 8.8Hz), 4.5- 4.9 (2H, m) and 7.26 (2H, d, J= 8Hz) — 7.36 (2H, d, J= 8Hz), 7.52 (1H, m), 7.61 (1H, dd, J= 1.5, 8Hz), 7.66 (1H, d, J= 1.5Hz), and 9. — 46, 9.06 (1H, bs), 10.86, and 10.43 (1H, bs) and 13.19 (1H, bs)
[0053] Example of reference 24-(2-[(ethoxycarbonyl) [(ethoxycarbonyl) oxy-] amino]-2-oxo-ethyl)-3-oxy—2-[4-(trifluoro methoxy) benzyl]-3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic-acid t-butyl ester [** 31]



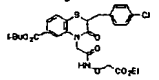
4-[2-(hydroxy amino)-2-oxo-ethyl]-3-oxy—2-[4-(trifluoro methoxy) benzyl]-3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid t-butyl ester (0.42g) 0.82mmol and N-methyl morpholine (182mg, 1.8mmol) were dissolved in THF (5ml), and under ice-cooling, ethyl chloroformate (195mg, 1.8mmol) was added, and to the room temperature, the temperature up was carried out and it was left all night. 5%-potassium-hydrogensulfate water solution was added and ethyl acetate extracted. A saturation sodium-hydrogencarbonate water solution and saturation brine washed the organic phase, and it dried with sulfuric anhydride magnesium. By filtering and removing a drying agent, refining a solvent after reduced pressure distilling off, and refining residue with a silica gel column chromatography (hexane: ethyl-acetate =6:1) 4-(2-[(ethoxycarbonyl) [(ethoxycarbonyl) oxy-] amino]-2-oxo-ethyl)-3-oxy—2-[4-(trifluoro methoxy) benzyl]-3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid t-butyl ester 520mg was obtained.
1 H-NMR(CDCl3, deltappm): 1.22-1.33 (6H, m), 1.53 (9H, s) 2.67 (1H, m) 3.33 (1H, m), 4.03 (1H, m) 4.35-4.41 (1H, m), 5.23-5.46 (2H, m) 7.22 (2H, br-s), 7.33 (2H, d, J=8.6Hz) 7.46 (1H, br-s) 7.54 (1H, d, J=8.1Hz) 7.59 (1H, d, J=8.1Hz)
[0054] Example of reference 34-[2-[[(allyloxy) Carbonyl] (hydroxy) Amino]-2-oxo-ethyl]-2-(4-chloro benzyl)-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid Allyl compound [** 32]



By the approach similar to an example 5 2-(4-chloro benzyl)-3-oxy—4-[2-oxy—2-[(tetrahydro-2H-pyran-2-yloxy) amino] ethyl]-3 obtained, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid Allyl compound Dichloromethane of (2.124g) (20ml) Bottom Nof ice-cooling-ethyl diisopropylamine (1.38ml) and a chloro formic acid allyl compound (677ul) were dropped to the solution. The temperature up was carried out to the 1 hour after room temperature, and it stirred all night. The reaction solvent was diluted with ethyl acetate after reduced pressure distilling off, water and saturation brine washed, and it dried with anhydrous sodium sulfate. The drying agent was filtered and removed, reduced pressure distilling off of the solvent was carried out, and the rough product was obtained. Then, the rough product was dissolved in the anisole (8ml), and the bottom trifluoroacetic acid (8ml) of ice-cooling was dropped. The temperature up was carried out to the after [10 minutes] room temperature, and it stirred for 2 hours. After reaction termination, toluene (30ml) was added and reduced pressure distilling off of the solvent was carried out. The actuation which furthermore adds toluene (30ml) and carries out reduced pressure distilling off was repeated 3 more times. residue — a silica gel column chromatography (ethyl acetate/hexane: 1/5) — refining — colorlessness — liquefied 4-[2-[[(allyloxy) Carbonyl] (hydroxy) amino]-2-oxo-ethyl]-2-(4-chloro benzyl)-3-oxy—3, 4-dihydro-2H-1, and 4-benzothiazin-6-carboxylic acid The allyl compound (2.04g) was obtained.
1 H-NMR (DMSO-d6, deltappm) : 2.76 (1H, m), 3.14 (1H, m) 4.02 (1H, m) 4.67-4.81 (6H, m), 5.24-5.41 (4H, m) 6.00 (2H, m), 7.23 (2H, d, J=8.43Hz) 7.31 (2H, d, J= 8.25Hz) 7.54 (1H, d, J=7.86Hz) 7.65-7.68 (2H, m) 12.59 (1H, br-s)
[0055] Example of reference 44-[2-[acetyl (acetyloxy) amino]-2-oxo-ethyl]-2-(4-chloro benzyl)-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid t-butyl [** 33]



2-(4-chloro benzyl)-4-[2-(hydroxy amino)-2-oxo-ethyl]-3-oxy-under nitrogen-gas-atmosphere mind - 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid After adding triethylamine (2.72ml) to the tetrahydrofuran (50ml) solution of t-butyl (3g), the acetyl chloride (1.15ml) was added under ice-cooling. It opened in saturation brine 3 hours after, and ethyl acetate extracted. Vacuum concentration of the oil reservoir was dried and carried out with the sodium sulfate. A silica gel column chromatography refines residue and it is 4-[2-[acetyl (acetyloxy) amino]-2-oxo-ethyl]-2-(4-chloro benzyl)-3-oxy-. - 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid t-butyl (3.1g) was obtained.
1 H-NMR(CDCl3, deltappm): 1.53-1.59 (9H, m), 2. 14 2.20 and 2.34-2.42 (6H, each s and m), 2.76 (1H, m) 3.27 (1H, m) 3.66 (1H, m), 4.81-5.28 (2H, m), 7.04-7.11 (2H, m), 7.24-7.27 (2H, m) 7.39 (1H, m) 7.43 (1H, s) 7.69 (1H, m)
[0056] Example of reference 52-(4-chloro benzyl)-4-[2-[(2-ethoxy-2-oxo-ethoxy) amino]-2-oxo-ethyl]-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid t-butyl [** 34]



2-(4-chloro benzyl)-4-[2-(hydroxy amino)-2-oxo-ethyl]-3-oxy-- 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid t-butyl (3g) was melted to THF (50ml), and 1-N sodium-hydroxide water solution (6.48ml) was added at 0

degree C. The actuation which adds and carries out vacuum concentration of the toluene to this was repeated 3 times. The obtained sodium salt (760mg) was suspended in the acetonitrile (5ml), bromoacetic acid ethyl (218microl) was added, and it stirred for 20 hours. The reaction mixture was diluted with water and ethyl acetate extracted. After saturation brine washed the organic layer, it dried with sulfuric anhydride magnesium. It is a silica gel column chromatography (it ranks second KISAN:ethyl-acetate =3:1 to 50g and solvent: silica gel:) about the residue which carried out the drying agent the ** exception and carried out vacuum concentration. It refines by 2:1. 2-(4-chloro benzyl)-4-[2-[(2-ethoxy-2-oxo-ethoxy) amino]-2-oxo-ethyl]-3-oxy— 3, 4-dihydro-2H-1, 4-benzothiazin-6-carboxylic acid t-butyl (460mg) was obtained as oily matter.
1 H-NMR(DMSO-d6, deltappm): 1.24 (3H, t, J=7.1Hz), 2.75 (1H, dd, J=8.7, 14.1Hz), 3.13 (1H, dd, J=6.6, 14.1Hz), 4.00 (1H, dd, J=6.8, 8.4Hz), 4.19 (2H, q, J=6.9Hz) 4.40-4.80 (4H, m), 7.19 (2H, d, J= 8.3Hz) 7.24 (2H, d, J=8.4Hz), 7.50 (1H, d, J=8.0Hz) 7.59 (2H, m) 11.18 and 11.77 (1H, each br-s)
[0057] The compound of the example of trial 1 oral-absorbency evaluation trial example 1 and the example 1 of reference was used, and kg was administered orally to 7 weeks old (Japanese CHARUSU liver) of Crj:CD(SD) system male rats in 30mg /under un-abstaining from food, respectively. After 1, 2, and 4 or 6-hour progress, it collected blood under anesthesia, the blood serum was obtained, and it saved below -20 degrees C to analysis for after [administration] 15 or 30 minutes. Acetonitrile 0.2ml was added to 0.2ml of blood serums, and centrifugal separation (15000rpm, 10 minutes) was carried out to them after churning. Supernatant liquid was analyzed by the ultra free-lancer (MILLPORE C3-HV), and 20micro of filtrate I was analyzed by liquid chromatography-mass spectrometry/MS after centrifugal filtration. The result of blood-drug-concentration transition of the compound of an example 1 and the example 1 of reference is shown in drawing 1 . From the test result of above-mentioned oral absorbency, it was checked that this invention compound is a prodrug with the oral absorbency which was excellent compared with corresponding hydroxamic acid.
[0058] Based on the well-known gene base sequence (Nature, 348, 699-704 (1990)) of Homo sapiens MMP-3, inhibition activity MMP-3 to example of trial 2MMP inhibition activity trial MMP-3 were prepared in gene engineering, and they used what was activated by holding at 37 degrees C for 16 hours under 4-aminophenyl mercury acetate existence of 1mM. Measurement of the inhibition activity over Homo sapiens MMP-3 was performed according to C.G.Knight's and others approach (FEBS Lett., 296(3) 263-266 (1992)). namely, 96 hole microplate for fluorometry -- the assay buffer (a 0.1M tris hydrochloric acid —) of 45microl 0.1M sodium chloride, 0.01M calcium chloride, 0.05% buri G 35, and pH=7.5 are put in. The dimethyl sulfoxide solution of the sample compound of 5microl is added. Activation ending Homo sapiens MMP-3 of 25microl, and 1mM (7-methoxy coumarin-4-IRU) Acetyl-L-prolyl-L-leucyl-glycyl-L-leucyl - L-[N-(2,4-dinitrophenyl)-L-2 and 3-diamino propionyl]-L-alanyl-L-arginine amide (MCA) Fluorescence (ex.320nm, em.405nm) was measured for the substrate solution which diluted the dimethyl sulfoxide solution with the assay buffer, and was set to 80microM with 25microl, in addition a fluorescence plate reader (made in a peptide lab). After holding for 2 hours and making it react at 37 degrees C, fluorescence was measured with the fluorescence plate reader and the enzyme activity which remains was measured.
[0059] the gene base sequence (J. — Biol.Chem. [ ] — 269 (24) —) of Homo sapiens MMP-13 with well-known inhibition activity MMP-13 to MMP-13 It is based on 16766-16773 (1994), and he is a gene engineering target (are made from a Homo sapiens chondrocyte cDNA library). Primer 5'-AATAAGCTTCCACCATGCATCCAGGGGTCCTGGC-3' It amplifies by PCR using 5'-CCGCTCGAGTTACCCCAAATGCTCTTCAGG-3'. It inserted in Vector pcDNAI, installation and a culture supernatant were prepared into African green monkey kidney origin COS-1 cell at recovery, and what was activated by holding at 37 degrees C for 2 hours was used under 4-aminophenyl mercury acetate existence of 1mM. Measurement of the inhibition activity over Homo sapiens MMP-13 was performed according to C.G.Knight's and others approach (FEBS Lett., 296(3) 263-266 (1992)). namely, 96 hole microplate for fluorometry — the assay buffer (a 0.1M tris hydrochloric acid —) of 45microl 0.1M sodium chloride, 0.01M calcium chloride, 0.05% buri G 35, and pH=7.5 are put in. The dimethyl sulfoxide solution of the sample compound of 5microl is added. Activation ending Homo sapiens MMP-13 of 25microl, and 1mM (7-methoxy coumarin-4-IRU) Acetyl-L-prolyl-L-leucyl-glycyl-L-leucyl - L-[N-(2,4-dinitrophenyl)-L-2 and 3-diamino propionyl]-L-alanyl-L-arginine amide (MCA) Fluorescence (ex.320nm, em.405nm) was measured for the substrate solution which diluted the dimethyl sulfoxide solution with the assay buffer, and was set to 80microM with 25microl, in addition a fluorescence plate reader (made in a peptide lab). After holding for 12 hours and making it react at 37 degrees C, fluorescence was measured with the fluorescence plate reader and the enzyme activity which remains was measured.
[0060] The inhibition activity Johnson and L.L. to MMP-1, and 2 and 9, Dyer R. and Hupe, D.J. Current Opinion in Chemical Biology, 2,466-471 (1998), Knight, C.G., Willenbrock F. and Murphy G FEBS Lett., 296 (3), 263-266 (1992) Olson, M.W. Gervasi, D.C., Mobashery, S. and Fridman, R., Biol.Chem., 272 (47), By the approach of 29975-29983 (1997), inhibition activity was measured on condition that the Table 1 publication.
[0061]
[Table 1]

	MMP-1	MMP-2	MMP-9
酵素の由来	ヒト	ヒト型遺伝子組み換え体	ヒト型遺伝子組み換え体
プレインキュベーション時間／温度	60分@37℃	60分@25℃	60分@25℃
インキュベーション時間／温度	2時間@37℃	3時間@25℃	2時間@25℃

To a substrate, both MMP-1, and 2 and 9 25microM (7-methoxy coumarin-4-IRU) Acetyl-L-prolyl-L-leucyl-glycyl-L-leucyl - an L-[N-(2,4-dinitrophenyl)-L-2 and 3-diamino propionyl]-L-alanyl-L-arginine amide 50mM(s) adjusted to the buffer for incubations pH=7.2 It carried out using a morpholino propyl sulfonic acid, 10mM calcium chloride, 10microM zinc chloride, and 0.05% buri G 35. The MMP inhibition activity of the compound of the example 1 of reference was shown. A result is shown in Table 2.

[0062]

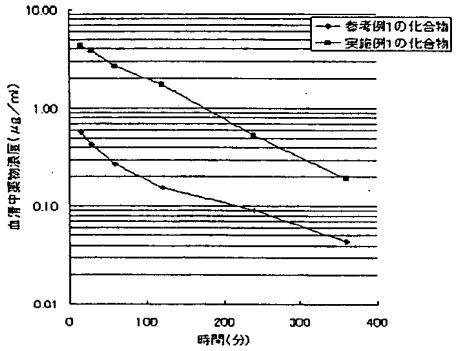
[Table 2]

MMP	MMP-1	MMP-2	MMP-3	MMP-9	MMP-13
阻害活性 (IC50/nM)	42	34	62	180	14

[0063]

[Translation done.]

Drawing selection drawing 1



[Translation done.]

CA data of Reference 4

L4 1 JP10084987/PN

=> D L4 BIB ABS

L4 ANSWER 1 OF 1 CA COPYRIGHT 2006 ACS on STN
AN 128:320657 CA Full-text
TI Manufacture of optically active α-hydroxy esters with bakers' yeast from α-keto esters
IN Yamano, Toru; Miwa, Katsuhiko; Kawada, Mitsuru
PA Takeda Chemical Industries, Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 10084987	A2	19980407	JP 1996-246687	19960918 <—
PRAI	JP 1996-246687		19960918		

OS CASREACT 128:320657; MARPAT 128:320657

AB Optically active RYm(CH2)nCHR1OC6H4ACH2CH(OH)CO2R4 [R = hydrocarbyl, heterocyclyl; Y = CO, CHOH, NR3; R3 = (un)substituted C1-4 alkyl; m = 0, 1; n = 0-2; R1, R4 = H, C1-4 alkyl; A = divalent C1-7 aliphatic hydrocarbyl; the benzene ring may be mono- or disubstituted] are manufactured by reduction of RYm(CH2)nCHR1OC6H4ACH2COCO2R4 (R, Y, m, n, R1, R4, A = same as above) in the presence of bakers' yeast and hydrolase inhibitors. The optically active compds. are useful as intermediates for antidiabetic oxazolidinediones. Bakers' yeast was treated with butanesulfonyl fluoride at 25° for 1 h in water, then treated with Et 5-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]-2- oxopentanoate at 25° for 18 h to produce the corresponding α-hydroxy ester with (R) form in 84.0% yield.